PHARMACOKINETIC STUDIES ON THE CONCOMITANT ADMINISTRATION OF PIPERACILLIN AND CEFAZOLIN, AND PIPERACILLIN AND CEFOPERAZONE IN RABBITS

TOSHIO HAYASHI, YASUO WATANABE, KATSUHIKO KUMANO, RIEKO KITAYAMA, TAKASHI YASUDA, ISAMU SAIKAWA, KYOICHI TOTSUKA†, TEPPEI KUMADA† and KIHACHIRO SHIMIZU†

Research Laboratory, Toyama Chemical Co., Ltd., Toyama, Japan

†Department of Internal Medicine, Tokyo Women's Medical College, Tokyo, Japan

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The pharmacokinetics of each drug on the concomitant administration of piperacillin (PIPC) and cefazolin (CEZ) or cefoperazone (CPZ) were studied in rabbits.

When rabbits received the consecutive drip infusion administration of CEZ (0.71 mg/kg/minute) and PIPC (1.38 mg/kg/minute) and likewise of CPZ (0.72 mg/kg/minute) and PIPC (1.54 mg/kg/minute) for 1 hour, respectively, the serum half-lives of CEZ and CPZ were respectively prolonged about 1.8 and 1.6 times during drip infusion of PIPC than administered alone. However, when the sequence of administration were reversed, the serum levels of PIPC were not affected by the consecutive drip infusion administration of CEZ and CPZ.

To study these findings in detail, the single intravenous dose of 20 mg/kg of CEZ and CPZ were administered under drip infusion of PIPC (2.65~2.93 mg/kg/minute). The serum half-lives of CEZ and CPZ were also prolonged about 5.4 and 1.9 times, respectively, whereas urinary excretion of CEZ, and urinary and biliary excretion of CPZ were reduced by PIPC. Moreover, when the single intravenous dose of 20 mg/kg of PIPC were administered under drip infusion administration of CEZ (0.96~2.60 mg/kg/minute), the pharmacokinetics of PIPC was not affected by the presence of CEZ. However, under drip infusion administration of CPZ (2.60~2.70 mg/kg/minute), the PIPC serum half-life was prolonged about 1.4 times, and biliary excretion of PIPC was reduced but urinary excretion was not.

From the results of renal clearance experiments, tubular secretion appeared to be the predominant mechanism of renal elimination for these three drugs.

These results indicate that PIPC influences the pharmacokinetics of both drugs by the competitively inhibiting tubular secretion in CEZ, and tubular secretion and hepatic transport system in CPZ. Therefore, in this respect PIPC seems to have probenecid-like action.

Combination antibiotic therapy is widely and commonly used in serious infection in immunocompromised patients as well as in mixed infection and is also used prophylactically in postoperative infection. The combination of two or more antibiotics, which provide broad spectrum of activity, has been extensively reported[1~9]. Although the combination of β-lactam antibiotics and aminoglycosides has often been used clinically, it is recognized that aminoglycosides have renal toxicity and ototoxicity[10~11]. However, β-lactam antibiotics have lower toxicity. Combination of β-lactam antibiotics, which have high antibacterial activity and broad spectrum, have therefore drawn an attention a clinical use. Nevertheless, there are only a little information on the pharmacokinetics of β-lactam antibiotics when concomitantly administered[12~15]. It is very important from the pharma-

cological and toxicological point of view to elucidate the pharmacokinetics of each drug on the concomitant administration of β-lactam antibiotics.

This paper deals with the pharmacokinetic change of each drug on the concomitant administration of piperacillin (PIPC) and cefazolin (CEZ), and PIPC and cefoperazone (CPZ) in rabbits.

Materials and Methods

Drug

Piperacillin (PIPC), cefoperazone (CPZ: Toyama Chemical Co., Ltd., Toyama, Japan), cefazolin (CEZ: Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan), inulin and sodium *p*-aminohippurate (PAH: Nakarai Chemical Co., Ltd., Kyoto, Japan) were commercial preparations. The antibiotics, inulin and PAH were dissolved in physiological saline.

Animals

Japanese white adult male rabbits weighing 2.8~3.4 kg were used.

Nature of Displacement

The extent of binding of CEZ and PIPC at various concentrations to rabbit serum were measured by the centrifugal ultrafiltration method reported previously[14]; *i.e.* CEZ and serum was incubated at 37°C for 1 hour, and fixed concentration of PIPC (final concentration: 5.8×10^{-4} M) was added to this mixture. After the incubation at 37°C for 1 hour, the binding rates of CEZ were determined. The binding rate of PIPC was also measured by mixing CEZ (final concentration: 5.8×10^{-4} M) with the same procedure. Similarly, the binding of CPZ and PIPC were determined with above mentioned procedure.

Drug Administration

Consecutive Drip Infusion Administration: Rabbits received a drip infusion administration at a dose of 1.45 mg/kg/minute of PIPC in the auricular vein for 1 hour, and then immediately received a dose of 0.74 mg/kg/minute of CEZ for 1 hour. Reversely, the consecutive drip infusion administration of CEZ (0.71 mg/kg/minute) and PIPC (1.38 mg/kg/minute) was also carried out. With respect to PIPC and CPZ, rabbits received a drip infusion administration of 1.49 mg/kg/minute of PIPC and 0.76 mg/kg/minute of CPZ, and the consecutive administration of CPZ (0.72 mg/kg/minute) and PIPC (1.54 mg/kg/minute) was carried out under the same procedure.

Intravenous Administration under Drip Infusion: PIPC was infused in the auricular vein at a dose of 0.97~2.93 mg/kg/minute throughout the experiments. At 45 minutes after infusion, CEZ or CPZ (20 mg/kg) were administered intravenously in auricular vein. Similarly, PIPC (20 mg/kg) was administered intravenously by drip infusion administration of CEZ (0.96~2.60 mg/kg/minute) or CPZ (2.60~2.70 mg/kg/minute). All infusions were made with an infusion pump (Atto Co., Ltd., Tokyo, Japan).

Collection of Specimens

Blood samples were withdrawn from auricular vein opposite to ear used for drug administration and were allowed to clot at room temp. Serum was then separated by centrifugation at $1,200\times g$ for 15 minutes. Urine and bile samples were taken by cannulating both the ureters and common bile duct. Samples were collected into 1/15 M phosphate buffer (pH 6.0) to avoid decomposition. Serum, urine and bile samples were stored at −20°C until just before assay.

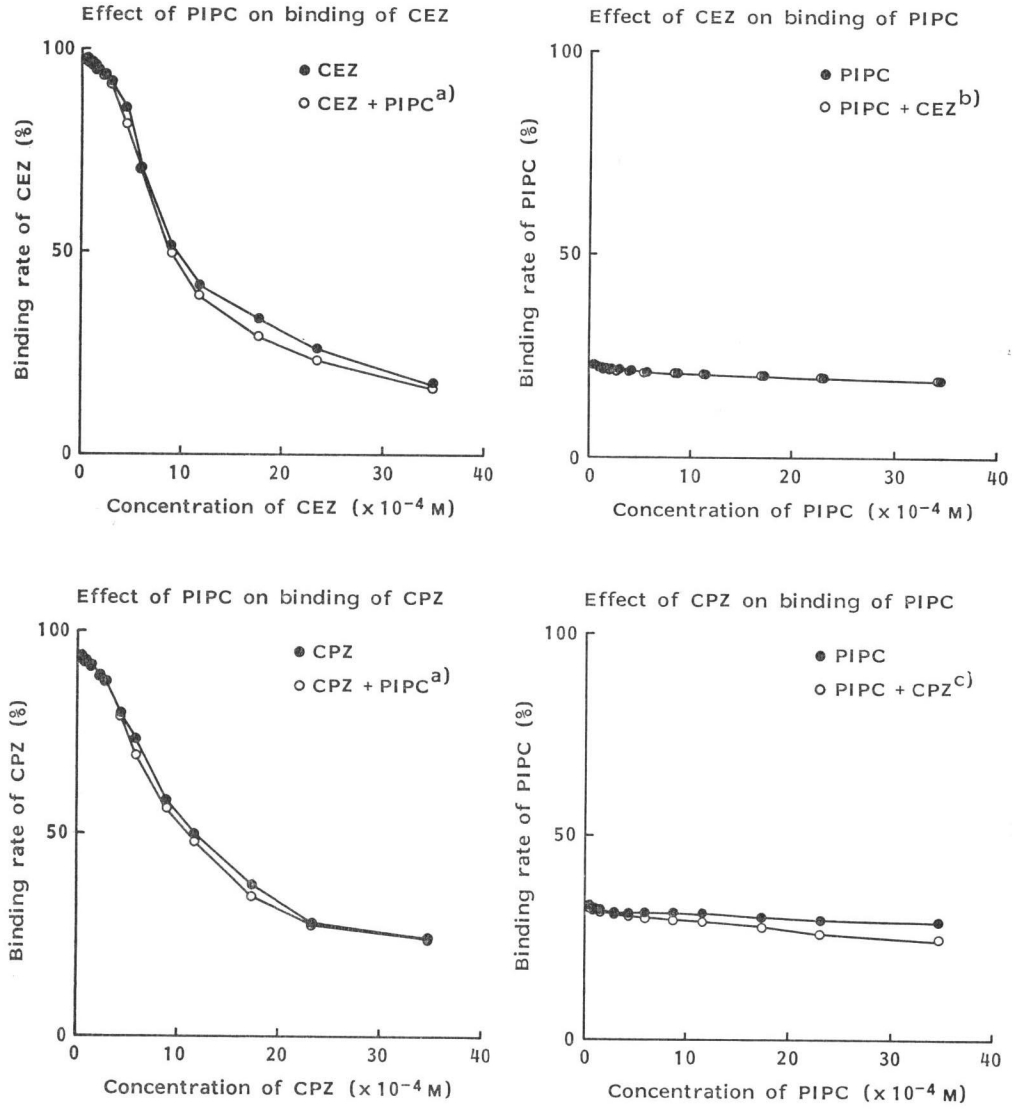
Measurement of Renal Clearance

Rabbits were anesthetized with ether. Polyethylene tubes were cannulated in auricular vein for drip infusion, right femoral artery for blood collection and both ureters for urine collection, respectively. After the operative procedures, the solution (0.5 g of PIPC, CEZ or CPZ, 2 g of inulin and 0.5 g of PAH in 1 liter of physiological saline) was infused with an infusion pump at the rate of 1 ml/minute per rabbit. Urine collection was started at 60 minutes after the initiation of infusion. Blood was collected in a heparinized syringe at the midpoint of urine collection, and the plasma was im-

Fig. 1. Competitive binding between CEZ, CPZ and PIPC to rabbit serum.

a) PIPC: 5.8×10^{-4} M (313 μg/ml), b) CEZ: 5.8×10^{-4} M (277 μg/ml), c) CPZ: 5.8×10^{-4} M (388 μg/ml).

Method: Centrifugal ultrafiltration. Final serum concentration: 90%.



mediately obtained by centrifugation ($1,200\times g$, 10 minutes at 4°C). Micro-partition system (MPS-1, Amicon Corporation, U.S.A.) was used for determination of unbound concentration in plasma.

Measurement of PIPC, CEZ, CPZ, PAH and Inulin

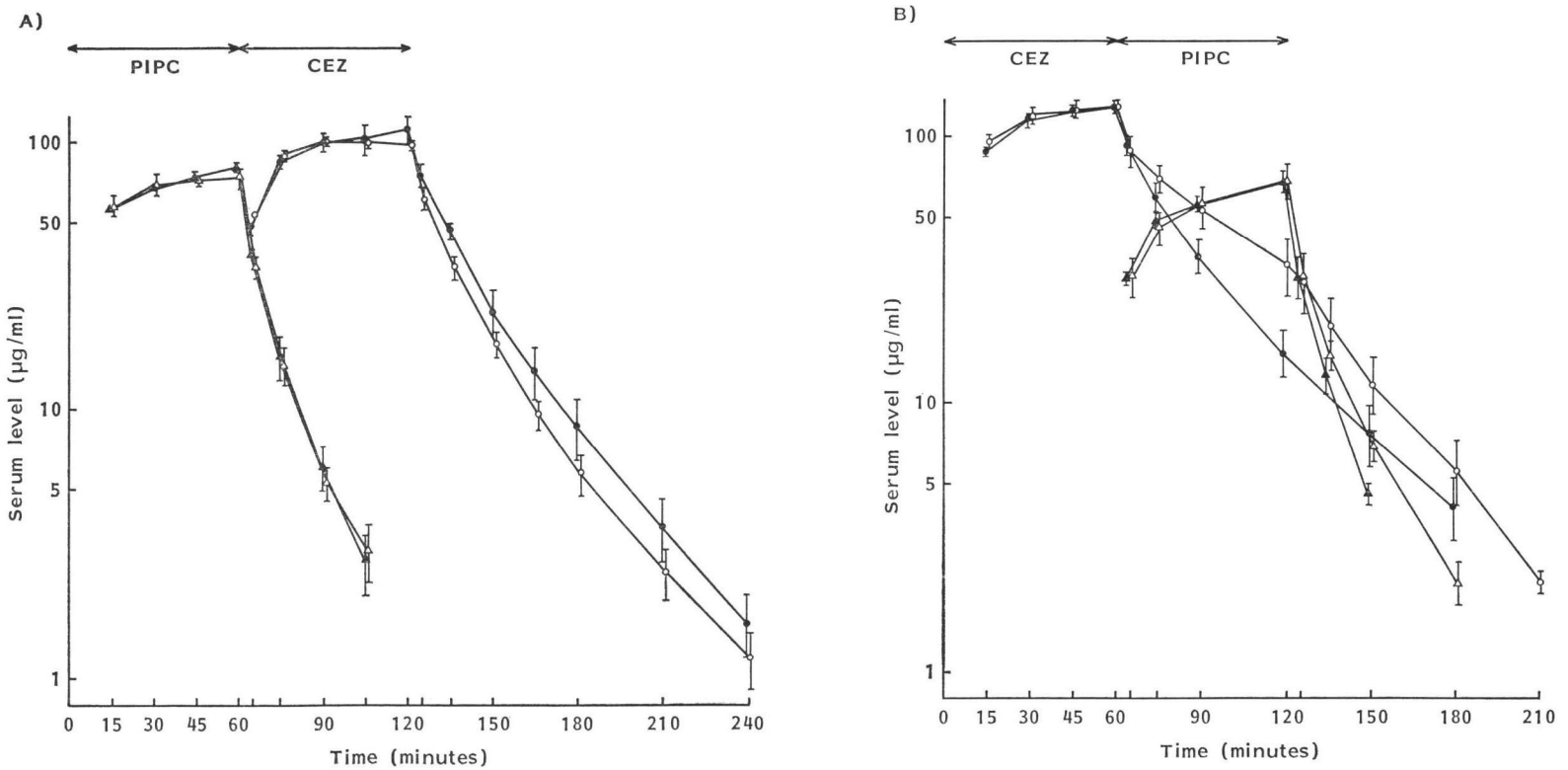
The concentrations of PIPC, CEZ, CPZ and PAH in serum, plasma, urine and bile specimens were assayed using high performance liquid chromatography (HPLC). Serum or plasma (0.5 ml) were added to 0.5 ml of methanol for deproteinization. The mixture was vigorously shaken for 30 seconds and centrifuged at $1,200\times g$ for 10 minutes at 4°C. The supernatant was separated and injected into HPLC. Urine and bile samples were filtered through 0.5 μm Milipore-filter and injected into HPLC. Samples were run on a column (300 mm×4 mm i.d.) of LiChrosorb RP-18 (10 μm: Merck) at an ambient temp with a flow rate of 2.0 ml/minute. The mobile phase consisted of 22% CH_3CN,

Fig. 2. Serum levels of PIPC and CEZ on the consecutive drip infusion administration in rabbits.
Each value indicates the mean±SE of 3~4 rabbits.

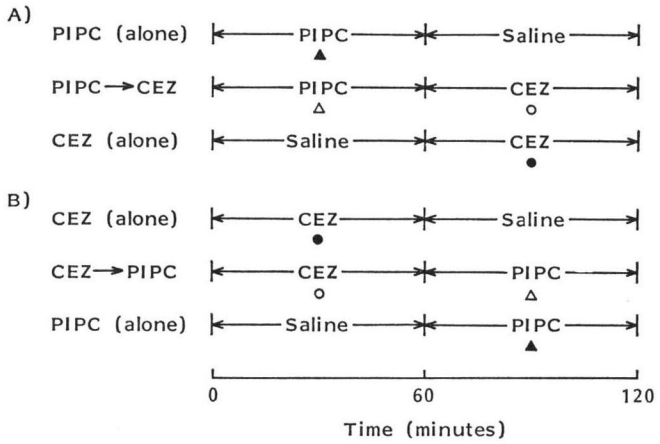
A) PIPC+CEZ: PIPC; 1.45 mg/kg/minute, CEZ; 0.74 mg/kg/minute. Alone: PIPC; 1.45 mg/kg/minute, CEZ; 0.78 mg/kg/minute.

B) CEZ+PIPC: CEZ; 0.71 mg/kg/minute, PIPC; 1.38 mg/kg/minute. Alone: CEZ; 0.69 mg/kg/minute. PIPC; 1.42 mg/kg/minute.

● CEZ (alone), ○ CEZ (+PIPC), ▲ PIPC (alone), △ PIPC (+CEZ).



Scheme 1. Administration schedule of PIPC and CEZ.
Rabbits received the consecutive drip infusion administration of PIPC and CEZ as following schedule.



1.4% 1 M CH_3COOH, 2.7% 1 M $(C_2H_5)_3N \cdot CH_3COOH$ in H_2O for PIPC in serum and plasma samples, 25% CH_3CN, 1.4% 1 M CH_3COOH, 2.7% 1 M $(C_2H_5)_3N \cdot CH_3COOH$ in H_2O for PIPC in urine and bile samples, 16% CH_3CN, 1.4% 1 M CH_3COOH, 2.7% 1 M $(C_2H_5)_3N \cdot CH_3COOH$ in H_2O for CEZ, 20% CH_3CN, 1.4% 1 M CH_3COOH, 2.7% 1 M $(C_2H_5)_3N \cdot CH_3COOH$ in H_2O for CPZ and 10% CH_3CN, 0.2% 1 M CH_3COOH, 3% 1 M CN_3COONa and 3 g of tetrabutylammonium bromide in H_2O for PAH. The eluate was monitored at 254 nm. Inulin concentrations were determined by photometric method reported by ROE *et al.*[16].

Pharmacokinetic Parameter

For the consecutive drip infusion administration, the serum half-life was determined from the last log linear segment of the serum concentration curve. For the intravenous administration under drip infusion, the pharmacokinetic parameter of each drug was calculated according to a 2-compartment open model[17].

Results

In Vitro Interaction between PIPC and CEZ, and between PIPC and CPZ

As shown in Fig. 1, the extent of binding of PIPC, CEZ and CPZ to rabbit serum were determined over a range of 5.44×10^{-5} M to 3.48×10^{-3} M as the final drug concentration. The binding rates of PIPC were not altered by the presence of CEZ or CPZ (5.8×10^{-4} M) and those of CEZ and CPZ were not altered by PIPC (5.8×10^{-4} M) either. No *in vitro* interaction between PIPC and CEZ and between PIPC and CPZ were detected.

Consecutive Drip Infusion Administration

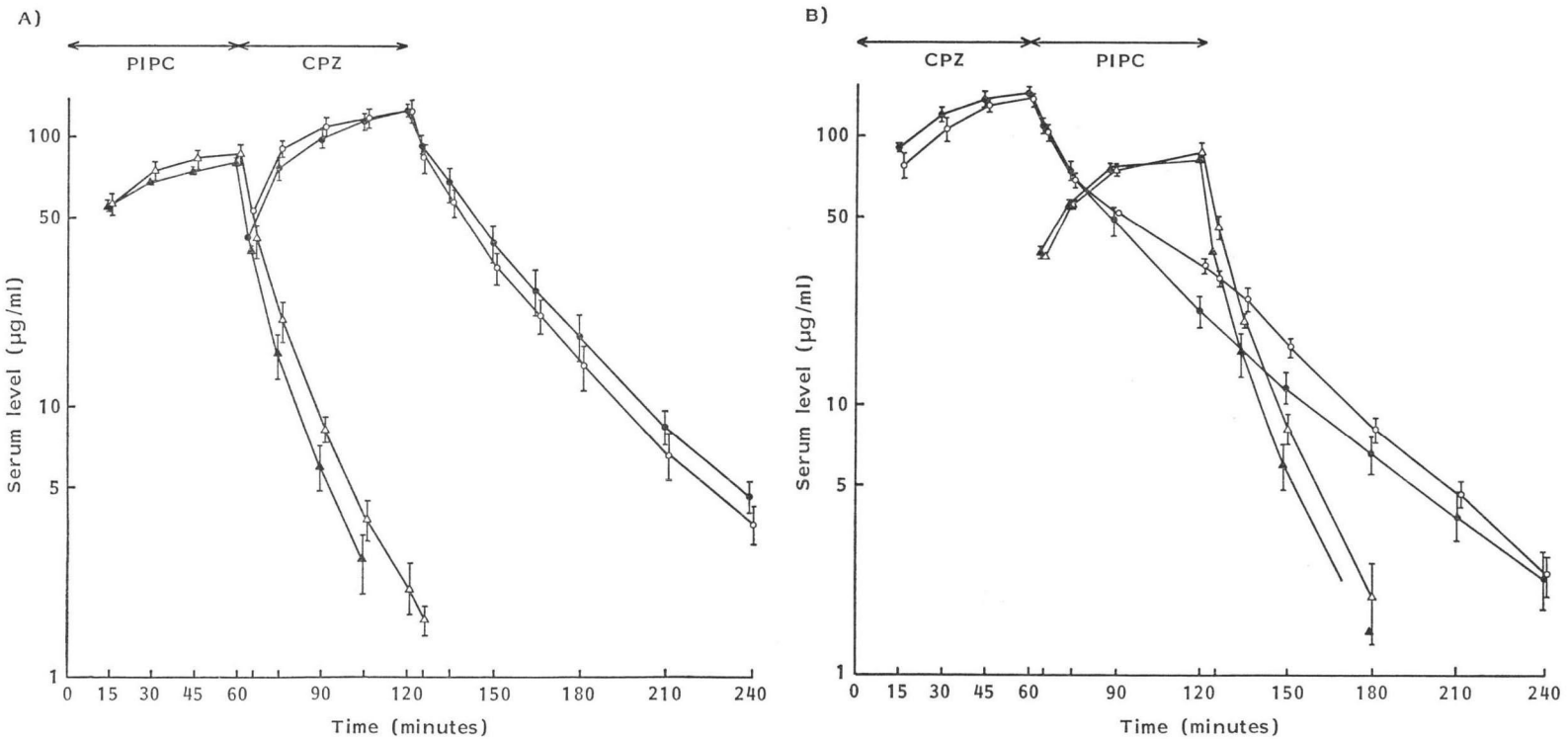
The serum levels of PIPC, CEZ and CPZ on the consecutive drip infusion administration are shown in Fig. 2 and Scheme 1, and Fig. 3 and Scheme 2. When PIPC and CEZ, and PIPC and CPZ were consecutively infused, the serum levels of PIPC were not affected by the consecutive drip infusion administration of CEZ and CPZ. Similarly, the serum levels of CEZ and CPZ were not affected by PIPC. On the contrary, when the administration sequence were reversed, the serum levels of CEZ and CPZ were elevated and its halflives were respectively prolonged about 1.8 and 1.6 times during drip infusion of PIPC as compared with the single administration. However, the serum levels of PIPC were not affected by the consecutive drip infusion administration of CEZ and CPZ.

Fig. 3. Serum levels of PIPC and CPZ on the consecutive drip infusion administration in rabbits.
Each value indicates the mean±SE 3~4 rabbits.

A) PIPC+CPZ: PIPC; 1.49 mg/kg/minute, CPZ; 0.76 mg/kg/minute. Alone: PIPC; 1.45 mg/kg/minute, CPZ; 0.77 mg/kg/minute.

B) CPZ+PIPC: CPZ; 0.72 mg/kg/minute, PIPC; 1.54 mg/kg/minute. Alone: CPZ; 0.73 mg/kg/minute, PIPC; 1.54 mg/kg/minute.

● CPZ (alone), ○ CPZ (+PIPC), ▲ PIPC (alone), △ PIPC (+CPZ).



Scheme 2. Administration schedule of PIPC and CPZ.
Rabbits received the consecutive drip infusion administration of PIPC and CPZ as following schedule.

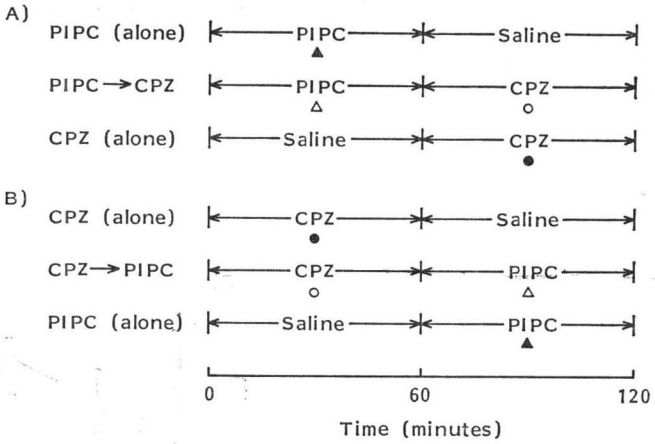


Fig. 4. Effect of PIPC on serum levels, and urinary and biliary excretion of CEZ in rabbits.
Each value indicates the mean±SE of 3~4 rabbits.

A) CEZ: 20 mg/kg, iv, PIPC (I): 0.97 mg/kg/minute, d.i., PIPC (II): 2.65 mg/kg/minute, d.i.
● CEZ (alone), △ CEZ (+PIPC (I)), ▲ PIPC (I) (+CEZ), ○ CEZ (+PIPC (II)),
■ PIPC (II)(+CEZ).

B) CEZ: 20 mg/kg, iv, PIPC: 2.84 mg/kg/minute, d.i.
● CEZ (alone), ○ CEZ (+PIPC).

* $P<0.05$. ** $P<0.01$.

d.i.: Drip infusion.

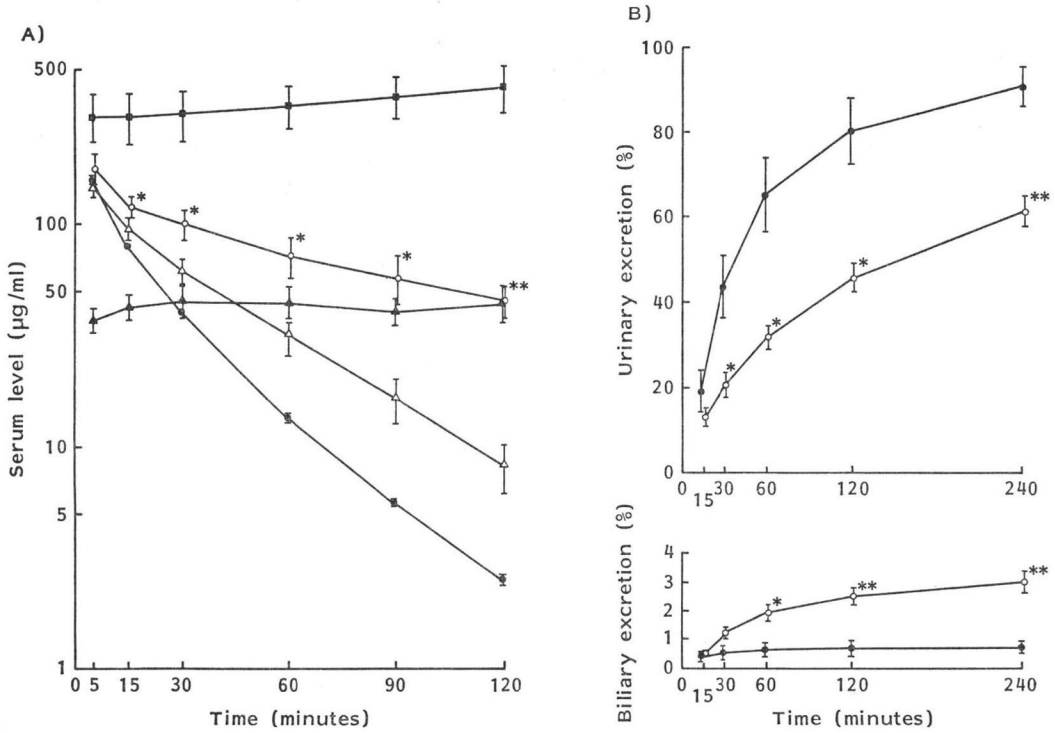
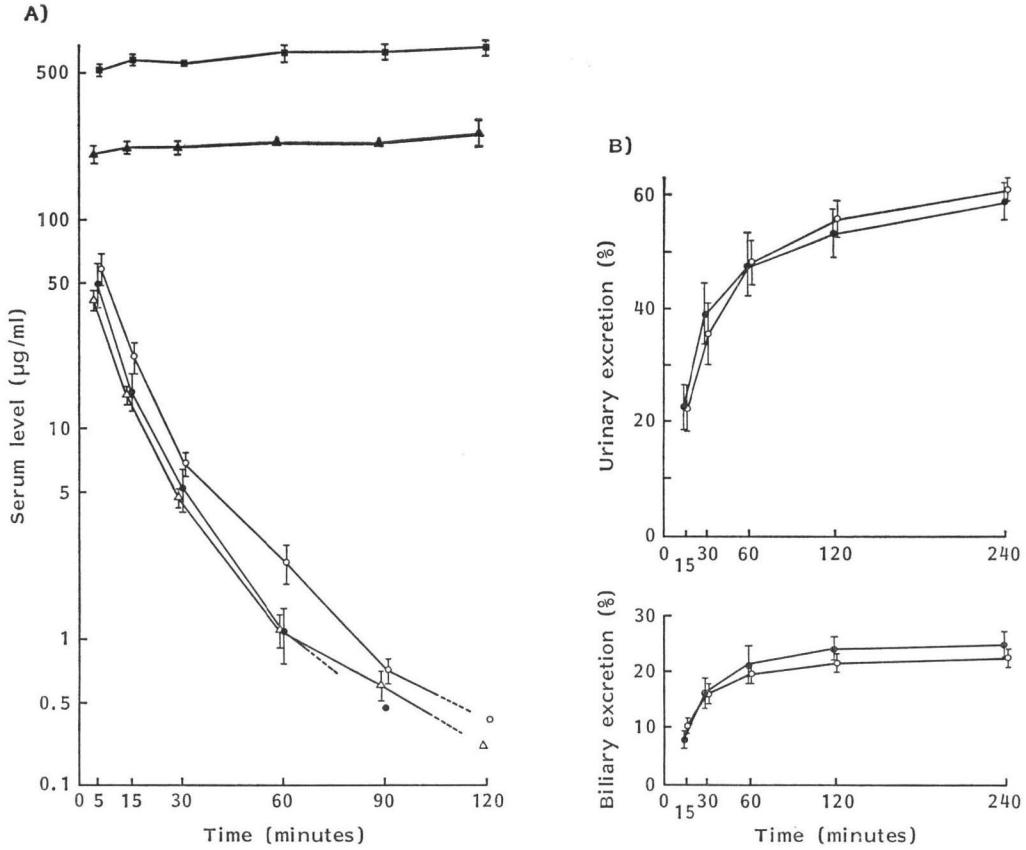


Fig. 5. Effect of CEZ on serum levels, and urinary and biliary excretion of PIPC in rabbits.
Each value indicates the mean±SE of 4~6 rabbits.
A) PIPC: 20 mg/kg, iv, CEZ (I): 0.96 mg/kg/minute, d.i., CEZ (II): 2.58 mg/kg/minute, d.i.
● PIPC (alone), △ PIPC (+CEZ (I)), ▲ CEZ (I) (+PIPC), ○ PIPC (+CEZ (II)), ■ CEZ (II) (+PIPC).
B) PIPC: 20 mg/kg, iv, CEZ: 2.60 mg/kg/minute, d.i.
● PIPC (alone), ○ PIPC (+CEZ).



Intravenous Administration under Drip Infusion

The serum levels, and urinary and biliary excretion of CEZ and PIPC are shown in Figs. 4 and 5, and the pharmacokinetic parameters are shown in Table 1.

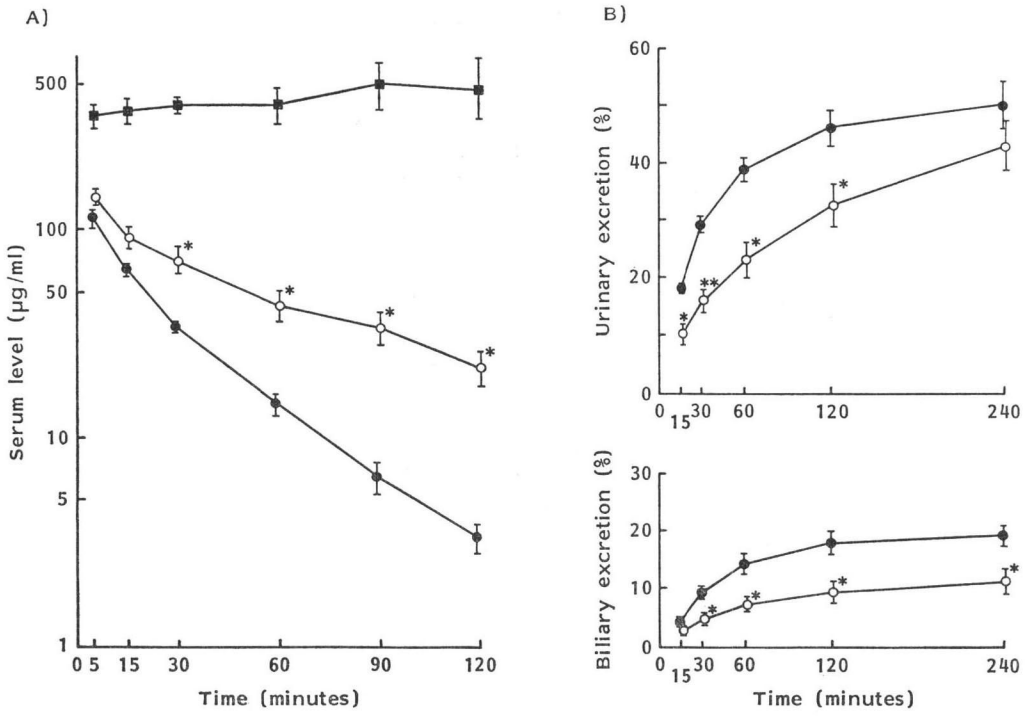
A single dose of 20 mg/kg of CEZ was administered intravenously under drip infusion of PIPC (dose I: 0.97 mg/kg/minute, dose II: 2.65 mg/kg/minute) (Fig. 4). The serum levels of CEZ under drip infusion of PIPC at dose I, were elevated as compared with the single administration of CEZ. The serum half-life of CEZ was 31.2 minutes, which was 1.5 times longer than that of single administration. With respect to the drip infusion of PIPC at dose II, high and prolonged serum levels of CEZ were observed as compared with those in the case of PIPC at dose I. The significant difference ($P<0.05$) were shown at all measured points, except for the point at 5 minutes after administration of CEZ. The serum half-life of CEZ was 109.8 minutes, which was 5.4 times longer than that of single dose administration. The serum half-lives and K_{el} values of CEZ on the concomitant administration of PIPC at dose I and II were significantly different from those of the single administration. How-

Table 1. Pharmacokinetic parameters of PIPC, CEZ and CPZ in rabbits.

	PIPC				CEZ			CPZ	
	Alone	+CEZ[a]		+CPZ	Alone	+PIPC		Alone	+PIPC
		0.96[b]	2.58	2.60		0.97	2.65		2.70
V (liter/kg)	0.246 ±0.054	0.284 ±0.058	0.209 ±0.051	0.23 ±0.02	0.080 ±0.009	0.100 ±0.007	0.075 ±0.030	0.14 ±0.02	0.109 ±0.014
K_{12} (hour^{-1})	2.30 ±0.37	1.47 ±0.55	1.78 ±0.47	1.71 ±0.63	2.59 ±0.79	2.45 ±0.66	9.93 ±7.40	1.68 ±0.42	2.71 ±0.44
K_{21} (hour^{-1})	4.62 ±0.89	2.54 ±0.62	3.05 ±0.03	3.18 ±0.78	5.26 ±0.88	6.96 ±2.33	4.11 ±1.55	3.74 ±0.80	3.89 ±0.42
K_{el} (hour^{-1})	7.04 ±0.47	6.11 ±0.85	5.78 ±0.76	4.58 ±0.89*	3.69 ±0.35	2.13 ±0.29*	1.47 ±0.65*	2.70 ±0.37	1.35 ±0.06*
$T_{1/2}$ (minute)	16.6 ±3.4	18.5 ±0.4	20.6 ±2.2	23.1 ±4.3	20.5 ±1.3	31.2 ±2.7*	109.8 ±15.0**	29.6 ±1.3	57.6 ±4.2*
Total clearance (ml/minute)	28.0 ±6.1	26.5 ±2.0	18.6 ±2.6	17.4 ±2.7*	4.8 ±0.1	3.5 ±0.5	1.2 ±0.2**	5.7 ±0.2	2.5 ±0.4*

[a] Under drip infusion administration of.
[b] mg/kg/minute.
* $P<0.05$.
** $P<0.01$.
Significant different from each single administration (alone).

Fig. 6. Effect of PIPC on serum levels, and urinary and biliary excretion of CPZ in rabbits.
Each value indicates the mean±SE of 3~5 rabbits.
A) CPZ: 20 mg/kg, iv, PIPC: 2.70 mg/kg/minute, d.i.
● CPZ (alone), ○ CPZ (+PIPC), ■ PIPC (+CPZ).
B) CPZ: 20 mg/kg, iv, PIPC: 2.93 mg/kg/minute, d.i.
● CPZ (alone), ○ CPZ (+PIPC).
* $P<0.05$. ** $P<0.01$.

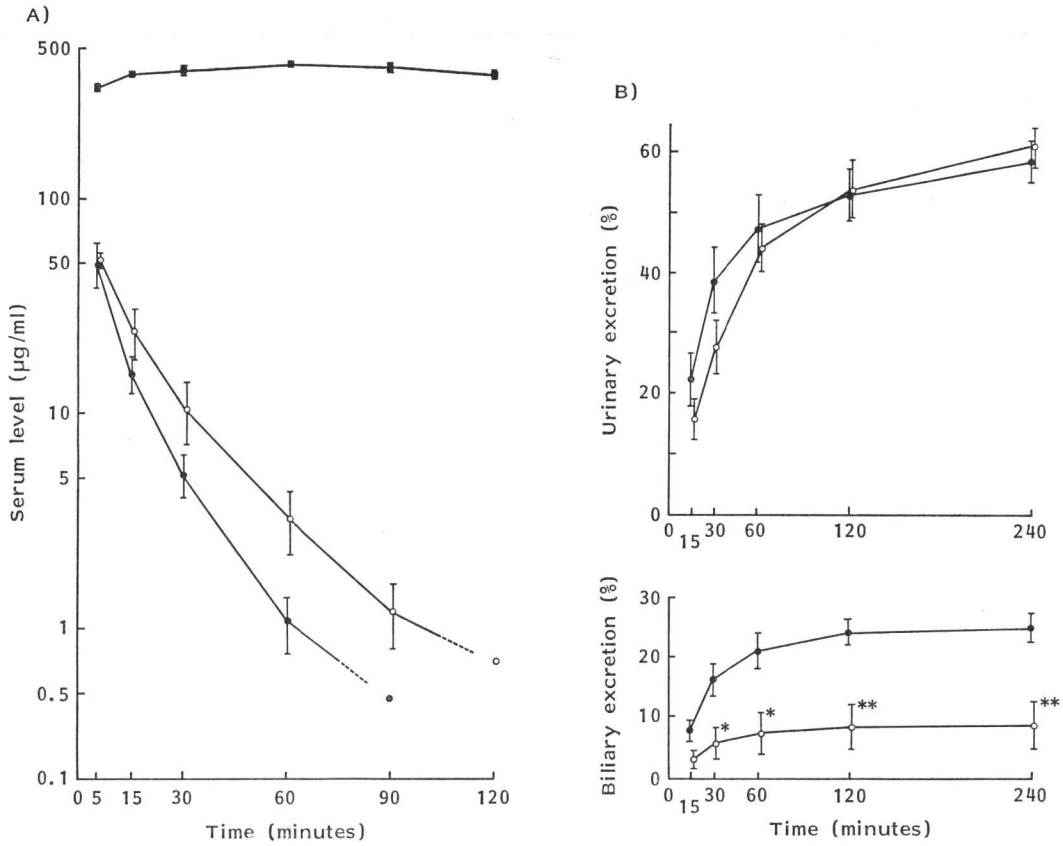


ever, no significant difference was found on other pharmacokinetic parameters. Urinary and biliary excretion of CEZ were determined in the presence of PIPC at a dose of 2.84 mg/kg/minute. The cumulative urinary excretion of CEZ on the concomitant administration of PIPC was 61.2±3.6% within 240 minutes, whereas on the single administration it was 90.8±4.6%. In contrast, biliary excretion of CEZ was 3.0±0.4% within 240 minutes under drip infusion of PIPC, whereas on the single administration it was 0.7±0.3% within 240 minutes. There were significant differences between these values.

A single dose of 20 mg/kg of PIPC was administered intravenously by drip infusion of CEZ (dose I: 0.96 mg/kg/minute, dose II: 2.58 mg/kg/minute). Under drip infusion of CEZ at dose I, the serum levels of PIPC were not affected by CEZ. In the case of drip infusion of CEZ at dose II, the serum levels of PIPC were slightly higher than those of the single administration (Fig. 5). Urinary and biliary excretion of PIPC under drip infusion of CEZ (2.60 mg/kg/minute) were also determined. The cumulative urinary and biliary excretion of PIPC were 60.8±2.3% and 22.3±1.6% within 240 minutes, respectively, whereas those of PIPC, when singly administered, were 58.6±3.5% and 24.7±2.4% within 240 minutes, respectively. No significant difference was found between the concomitant and single administration on urinary and biliary excretion of PIPC.

Figs. 6 and 7 show the serum levels, and urinary and biliary excretion of PIPC and CPZ.

Fig. 7. Effect of CPZ on serum levels, and urinary and biliary excretion of PIPC in rabbits.
Each value indicates the mean±SE of 3~6 rabbits.
A) PIPC: 20 mg/kg, iv, CPZ: 2.60 mg/kg/minute, d.i.
● PIPC (alone), ○ PIPC (+CPZ), ■ CPZ (+PIPC).
B) PIPC: 20 mg/kg, iv, CPZ: 2.70 mg/kg/minute, d.i.
● PIPC (alone), ○ PIPC (+CPZ).
* $P<0.05$. ** $P<0.01$.



The serum levels of CPZ under drip infusion of PIPC were significantly high at all point in time after 30 minutes post administration. The serum half-life was prolonged about 1.9 times. The cumulative urinary and biliary excretion of CPZ, when singly administered, were 50.1±4.1% and 18.9±1.9% within 240 minutes, respectively. However, those in the presence of PIPC were 42.8± 4.3% and 11.0±2.1%, respectively. Urinary and biliary excretion of CPZ was significantly reduced in the presence of PIPC. On the other hand, the serum levels of PIPC under drip infusion of CPZ were slightly elevated and its serum half-life was prolonged about 1.4 times. The cumulative urinary excretion of PIPC within 240 minutes was similar to that of the single administration, but biliary excretion was significantly reduced, as compared with PIPC alone. The V (apparent distribution volumes), K_{12} and K_{21} values of PIPC and CPZ on the concomitant administration were not different from those on the single administration. The serum half-lives of PIPC and CPZ under drip infusion were increased more than that of each drug alone, whereas total clearance and K_{el} values of PIPC and CPZ were significantly decreased, as compared with those for the single administration (Table 1).

Table 2. Renal clearance of PIPC, CEZ and CPZ in rabbits.

	Plasma concentration (μg/ml)		F[a]	T[b]	Renal clearance (ml/minute)	
	Total	Free	(%)		C_{total}[c]	C_{free}[c]
PIPC	11	7.74	19	81	27.8	39.8
CEZ	52	5.00	9	91	9.21	109
CPZ	32	2.15	15	85	3.40	50.3

[a] F: (Glomerular filtration)/(urinary excretion) × 100.
[b] T: (Tubular secretion)/(urinary excretion) × 100.
[c] C: Renal clearance rate.

Renal Clearance

The results of the renal clearance experiments are shown in Table 2.

From the ratio of tubular secretion to urinary excretion, tubular secretion was the main renal elimination route for PIPC, CEZ and CPZ.

Discussion

We previously reported the *in vitro* interaction of two β-lactam antibiotics on the serum protein and pharmacokinetic changes after simultaneous administration in rabbits and humans. CEZ and CPZ competed with each other for the binding sites on rabbit and human serum protein. Moreover, when CEZ and CPZ, which have high binding rates to serum protein, were simultaneously administered, the serum levels of each drug were reduced and subsequently excretion in urine were increased due to the elevated level of unbound drug, as compared with that for single administration[14]. The changes in the serum protein binding rate and pharmacokinetics were also observed for apalcillin and CEZ or CPZ[15]. On the other hand, the pharmacokinetic changes of novobiocin and CEZ or CPZ were not reflected on the results of *in vitro* interaction to serum protein[16]. These results suggested that *in vitro* interaction to serum protein was not always reflected on the pharmacokinetic changes.

In the present paper, we investigated the interaction between PIPC, which has low binding rate to serum protein, and CEZ and between PIPC and CPZ, which were excreted from renal and hepatic route, on the concomitant administration in rabbits. The binding rates of PIPC to rabbit serum were not affected by CEZ and CPZ, and both CEZ and CPZ were not affected by PIPC. The main binding site of PIPC on serum protein seemed to be different from that of CEZ and CPZ. These *in vitro* results indicated that the pharmacokinetic changes of CEZ and CPZ by the concomitant administration of PIPC were not induced by the competitive inhibition of binding to serum protein.

As shown in Figs. 4 and 5 and Table 1, the serum levels of CEZ was elevated and serum half-life was prolonged, whereas urinary excretion of CEZ was reduced by the concomitant administration of PIPC. On the other hand, PIPC was not affected by the concomitant administration of CEZ. PIPC and CEZ were found to be eliminated mainly by renal tubular secretion. From these results the decrease of urinary excretion for CEZ can not be explained by the saturation of PIPC at the renal secretion system. If the prolongation of serum levels and decrease of urinary excretion of CEZ in the presence of PIPC could be explained by the saturation of PIPC, the serum half-life and urinary excretion of PIPC under drip infusion of CEZ should be prolonged and reduced, respectively, as well as CEZ. But as shown in Fig. 5, the pharmacokinetic change of PIPC was not observed. These results therefore suggest that the interference of PIPC on the pharmacokinetics of CEZ seems to be due to competitive inhibition of renal tubular secretion.

As shown in Figs. 6 and 7, CPZ serum levels were significantly elevated and prolonged by the presence of PIPC, whereas both urinary and biliary excretion were significantly reduced. Moreover, tubular secretion appeared to be the predominant mechanism of renal elimination for CPZ, as well as PIPC and CEZ. Therefore, the interference of PIPC on the serum levels of CPZ shown in Fig. 6 seems to be explained by the competitive inhibition of tubular secretion and hepatic transport system.

On the other hand, the prolongation of the half-life of PIPC under drip infusion of CPZ is mainly due to competitive inhibition of hepatic transport system but not renal tubular system. From these results, the interference of PIPC by CPZ and that of CPZ by PIPC on biliary excretion may be explained by the saturation of drug at hepatic transport system. But the interference on urinary excretion can not be explained by the saturation of drug at the renal tubular secretion system. These results show that PIPC is apparently superior to CEZ and CPZ in the competition and appears to have a higher affinity for the tubular secretion system. Therefore, PIPC appears to have the activity of inhibiting tubular secretion like probenecid.

These results suggest that renal excretion mechanism and selectivity of drug in renal excretion have to be taken into consideration as important factors to investigate the pharmacokinetics. YAMAZAKI *et al.*[19] have showed that cefmenoxime (CMX), CEZ, cefotaxime (CTX) and cefotiam (CTM) were largely excreted by tubular secretion system in rabbits, and cefsulodin (CFS) by glomerular filtration. If PIPC were concomitantly administered with CMX, CTX or CTM, PIPC might influence the pharmacokinetics of these drugs as well as CEZ. Moreover, it is interest to investigate how the pharmacokinetics of PIPC and CFS are affected when both drug are co-administered.

Further studies concerning the pharmacokinetics on the concomitant administration of β-lactam antibiotics in human remain to be conducted.

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